Remarks/Arguments

The courtesy of telephone interview with the Examiner May 19, 2006 is acknowledged with appreciation. Applicants also acknowledge a further interview with the Examiner for the purpose of clarifying the election August 29, 2006 wherein clarification of the Office Action dated August 10, 2006 with respect to the election was discussed. No claims or references were discussed August 29, 2006.

Applicants respectfully traverse the restriction requirement that only one drug should be considered for examination purposes. Applicants consider that many of these drugs are related and while there is always some reservation as to the effect of each drug independently and exclusively of the others, it is respectfully submitted that many of these drugs are included in classes of drugs having similar properties and it is also noted that Applicants have performed tests on various of the drugs in various of the classes in addition to the tests shown in this application. These tests could be submitted under 132 Affidavits.

The omission of a claim 28 from the claims is acknowledged and withdrawn of this claim is acknowledged.

The Examiner has stated that claims 1-5, 7-27 and 29-51 are under consideration. As noted previously Applicants have amended, cancelled and acknowledged as cancelled or withdrawn various of the claims without prejudice, with the claims presently shown as being pending being claims Applicants consider to be now present in the application.

The acknowledgement of Applicants' claim for priority under 35 U.S.C. 120 is acknowledged with appreciation.

It is believed that the amendment to claim 30 has overcome all objections to this claim.

It is also believed that Applicants' amendments to claim 25 and the cancellation of claim 8 have obviated all rejections of claims under 35 U.S.C. 112.

The Examiner's rejection of Applicants' claims 35-51 under 35 U.S.C. 112 as not enabled by the disclosure is respectfully traversed, particularly in view of the fact that the examination of Applicants' claims has now been limited to a single drug, i.e., budesonide. It is respectfully submitted that the tests shown in Applicants' specification are more than adequate to enable one skilled in the art to perform the method set forth in claims 35-51. It is

hard to believe that anyone skilled in the art could not review Applicants' specification and prepare the materials necessary and administer the materials as disclosed in Applicant's specification. It appears that no experimental work is necessary to make or use the invention as presently claimed in view of the required restriction.

The Examiner's restriction in this regard appears to be based primarily upon the presence of claims which include more drugs than the required budesonide. While it is understood that many of these drugs may be subject to allowance upon the finding of an allowable generic claim, it is respectfully submitted that the claims as presently claimed are not subject to this objection by the Examiner.

The Examiner's discussion of the state of the art is noted. The reference to Deol, et al Biochimica et Biophysica Acta11334:161-172, is noted. The use of stealth liposomes for injection into the blood stream or other tissue is well known. In fact, as indicated in Applicant's specification these materials used by Applicants were obtained commercially and combined as shown by the Applicants to produce the claimed carrier having the unexpectedly superior results. Similarly U.S. Patent 6,197,333B1 issued March 6, 2001 to Onyuksel, et al (Onyuksel) teaches no more than a method for using stealth liposomes in a different type of process. The remainder of the discussion appears to be a very generalized discussion which is believed to be primarily obviated by Applicants' claim amendments. The discussion of the broad sweep of the prior art does not appear to be particularly relevant in view of the amendments to Applicants' claims.

The rejection of Applicants' claims 1-4, 7-14, 16-27, 29-31 and 33-34 under 35 U.S.C. 102(b) as anticipated by Onyuksel is respectfully traversed and reconsideration is respectfully requested.

As pointed out previously and in response to the Examiner's first comment, the claims are now drawn to budesonide. In other words, as directed to a specific drug as required in the restriction. As a result the generalization that any drug is useful is not considered appropriate at this point. The Examiner first points out that Onyuksel teaches a method to make sterically stabilized liposomes. These materials were well known to those skilled in the art many years before the Onyuksel reference. Applicants have so acknowledged.

Applicants have noticed with some interest the breadth of the claims granted on Onyuksel in view of the onerous restrictions the present Examiner has imposed on the Applicants. For instance, biologically active amphipathic compounds appear to be very, very broad, yet the Patent Office found this term to be acceptable. The liposomes discussed apparently have a diameter of less than about 300 nanometers, which is considerably larger than Applicants' preferred sizes. Further the term "biologically active amphipathic compound" is clearly broader than can be enabled by the specification. Accordingly the specification disclosure must be limited to those materials disclosed as meeting this definition.

Applicants have reviewed this reference and it is believed clear that no budesonide is discussed. It is also believed clear that there is no administration of this material as an aerosol. Applicants in Onyuksel have attempted to cover the waterfront by reciting that the liposome products of the invention may be administered intravenously, intraarterially, intranasally, such as by aerosol administration, nebulization, inhalation or insufflation, intratracheally, intra-articularly, orally, transdermally, subcutaneously, topically onto mucous membranes, such as, but not limited to oral mucosa, lower gastrointestinal mucosa and conjunctiva, and directly onto target tissues. It is clear that the target tissues do not include the lungs and it is submitted that there is no disclosure of how this material might be administered as an aerosol. Please note the examples wherein different forms of administration were used. It appears clear that this material is injected intravenously. The material is injected to treat a different problem than Applicants purport to treat and was injected apparently by directly positioning in a cheek pouch membrane of a hamster. There is no suggestion in this reference that extended life of the treatment has been extended to anything approaching the extension of the effective treatment time by the Applicants' claimed invention. There is no showing of mammalian lung compatibility.

In conclusion, there is absolutely no suggestion in this reference and there is no showing in this reference of Applicants' claims 1-4, 7-14, 16-27, 29-31 and 33-34, especially as considered with the limitation to budesonide. More specifically there is no showing in this reference of any material which has been demonstrated to be compatible with the respiratory tract of a mammal and effective to extend the effective life of budesonide in the respiratory

tract of a mammal by a time equal to at least twice the effective life of the budesonide alone. Specifically, this reference does not disclose the effectiveness of the composition and it is respectfully suggested that the composition as more precisely defined has been shown to achieve a function which has not been achieved by Onyuksel.

Accordingly, it is respectfully submitted that Applicants' claims 1-4, 7-14, 16-27, 29-31 and 33-34, even as originally submitted, have not been shown or suggested by Onyuksel and certainly there has been no showing of these claims as presently amended to include budesonide.

It is further noted that Onyuksel includes a number of materials which Applicants do not consider suitable for instance, the use of sphingomyelin. It is noted that Onyuksel says that polymers of the invention may include any compounds known and routinely utilized in the state of SSL (sterically stabilized liposomes) technology and technologies which are useful for increasing the circulatory half-life for proteins, including for example, polyvinyl alcohol, polylactic acid, polyglycolic acid, polyvinylpyrrolidone, polyacrylamide, polyglycerol, polyaxozlines, or synthetic lipids with polymeric headgroups. The preferred lipids are referred to as distearoyl-phosphatidylethanolamines covalently bonded to poly (ethylene glycol), which is a well known material for the introduction of poly (ethylene glycol) into a liposome create a stabilized liposome or mixture of liposomes.

Onyuksel shows preparations for sterilized liposome materials but is primarily directed to use with peptides rather than other drugs. Onyuksel only claims preformed liposomes to which amphipathic peptides are added. Thus, the peptides are not included during the preparation of the liposomes. This method is very different from the method shown by Applicants. The liposome preparations are disclosed to be a promising therapeutic agent for a number of ailments but no enablement for this is demonstrated.

Onyuksel is long on hypotheses but relatively short on supporting information. It is respectfully submitted that no enablement is shown beyond the sparse examples provided for the wide-sweeping conclusions in the reference. It is again, respectfully submitted that this reference does nothing to show or suggest Applicants' claimed invention.

The rejection of Applicants' claims 1, 5, 14-15, 18, 31-32 and 35 -51 under 35 U.S.C. 103 as unpatentable over U.S. Patent 5,958,378A issued September 28, 1999 to Waldrep, et

al (Waldrep, et al) as applied to the limitation of a liposome carrier and the drug budesonide and in further view of Onyuksel as applied respectively to the limitations of sterically stabilized liposomes with the respiratory tract of a mammal and a drug as evidenced by Konduri, et al. (Journal Allergy Clinic Immunology, Supplement 107(2): S315, 2001 (Konduri) and Waldrep (Waldrep), Abstract only, June, Drugs Today 34(6): 549-561, 1998. Waldrep is respectfully traversed and reconsideration is respectfully requested.

Onyuksel fails to disclose or suggest Applicants' claimed invention for the reasons discussed above. Particularly the reference does not use budesonide, it does not appear to be administerable as an aerosol, it does not disclose any composition suitable for use in the lungs of a mammal; it does not show that any extended life is obtained for the drug and is generally dissimilar to Applicants' invention as now claimed. It appears particularly that this reference is directed to peptides, although it is written in such broad sweeping language that it attempts to cover a broad universe of formulations. However, the disclosure must be restricted to those materials which are shown and enabled to be used by those skilled in the art.

Waldrep, et al discloses a high dose budesonide or cyclosporine A composition in a liposome aerosol which is formulated to be dispersible as an aerosol. There appears to be no suggestion in this reference that sterically stabilized liposomes could or should be used. Accordingly these liposomes are not comparable to the liposomes used by Applicants and there is no suggestion in Waldrep, et al. that these materials could be used in combination with budesonide with a carrier comprising phosphatidylcholine, phosphatidylglycerol and poly (ethylene glycol) to achieve the surprisingly superior results achieved by Applicants. Accordingly Waldrep, et al., since it does not use sterically stabilized liposomes, does nothing to add to the disclosure in Onyuksel.

The suggestion that the abstract of Konduri, et al (Konduri) fulfills this shortcoming is respectfully traversed. Konduri discloses the use of a sterically stabilized liposome in conjunction with budesonide. However, Konduri does not disclose any specific formulation for the sterically stabilized liposome and therefore does not enable those skilled in the art to practice the procedure disclosed in the abstract. This reference also fails to enable the production of the sterically stabilized liposome required in Applicants claims as presently

amended. These claims require that the sterically stabilized liposome include poly (ethylene glycol). It is also required that these materials be compatible with the lungs of a mammal and effective to extend the effective life of a drug (budesonide) in the respiratory tract of a mammal for a time equal to at least twice the effective life of the budesonide.
The abstract by Waldrep appears to be primarily prophetic. It suggests that drugs might be injected into the lungs using a composition which is not disclosed and which may include a variety of drugs other than budesonide. There is no disclosure that effectiveness has been accomplished and the abstract is very general (not enabling) and prophetic.

The Examiner has concluded that it would be obvious to one of ordinary skill in the art to substitute the biologically active compounds taught by Onyuksel with budesonide as taught by Waldrep, et al. It should be noted that Onyuksel is directed to methods which are shown in the examples to comprise injection of the disclosed drugs into tissues or blood streams. There is no suggestion in Onyuksel, as discussed previously, that aerosol treatments should be used.

The Waldrep abstract hypothesizes that liposomes may be used for aerosol delivery. However, this reference does not use stealth liposomes which are well known to those skilled in the art to have radically different properties than liposomes which have not been treated by exposure to materials which extend their life in a bloodstream. Conventional (i.e., non-sterically stabilized) liposomes have not been effective to obtain the extended drug life of Applicants' claimed invention, a finding which has now been published.

Waldrep, et al. discloses compositions for putting high doses of liposome in aerosol compositions for use in an aerosol. This reference is primarily directed to improved methods for inhalation. As noted previously, this reference does not disclose the use of sterically stabilized liposomes. Since the materials used are selected specifically for their inhalation properties, it is not reasonable to believe by those skilled in the art that other materials could be substituted.

Konduri has been cited as showing the use of sterically stabilized liposomes in conjunction with budesonide for use in the treatment of mice. No composition is disclosed in Konduri beyond the use of the sterically stabilized liposomes with budesonide for the treatment of mice. It is respectfully submitted that Waldrep, et al. does not suggest that any

materials other than liposomes (not sterically stabilized liposomes) could be produced in concentrated form for improved aerosol use. Waldrep, et al. does, however, raise the issue that it is not automatically given that compositions comprising liposomes with drugs will be effective for use as an aerosol. The Examiner has reached the conclusion that Waldrep, et al. is readily combined with Onyuksel with no real basis other than the fact that they both name individual materials which may be used in Applicants' claimed invention. While Onyuksel discloses the use of stabilized liposomes in a composition, there is no suggestion that the composition could be used as an aerosol, therefore, it is appears illogical to conclude in view of the difficulties discussed in Waldrep, et al that this substitution could be made.

As noted, Konduri does not disclose any specific composition which was used in her tests. Accordingly, it is respectfully submitted that these references taken in combination do not disclose or suggest to those skilled in the art a carrier composition as specifically defined in Applicants' claims which can be used with a drug such as, in this instance budesonide, to produce a material which can be administered as an aerosol which is compatible with the respiratory tract of a mammal and effective to extend the effective life of a drug up to twice the life of the drug alone. There is no suggestion in any of these references that such extended life could be achieved.

It is further pointed out that this rejection is based upon reaching and selecting specific disclosures from each of four separate and unrelated references. No attention has been given as to whether these references are properly combinable and it is respectfully submitted that they are not combinable and even if combined, do not show or suggest Applicants' claims as amended.

Neither Onyuksel nor Waldrep, et al. is directed to the treatment of the respiratory tract of a mammal by the use of a carrier composition comprising phosphatidylcholine, phosphatidylglycerol and poly (ethylene glycol). More specifically Onyuksel is directed to the production of a mixture comprising, among other things, peptides, for use by injection into a tissue or bloodstream. There is no suggestion that this material would be useful as an aerosol. Similarly, Waldrep, et al. discloses a procedure and a composition which they consider to be more effective for the injection of a liposome (not sterically stabilized liposome) into the lungs by an aerosol procedure. There is no suggestion in Waldrep, et al

that this composition is effective. Furthermore it does not contain all of the components required in Applicants' claimed composition nor does it produce the results produced by Applicants' claimed composition. It should be noted also that Onyuksel teaches liposomes to which the peptide drug is added after the liposomes are prepared, a procedure different than that taught by Applicants.

The Konduri abstract does not disclose the composition used with the treatment of the mice. Accordingly, this reference fails to enable those skilled in the art to practice the invention. Furthermore, even if this reference is substituted into the other references, it is conjectural as to why such a substitution should be made since each of the references is presumed effective for the purpose for which it is issued and there is no good reason to substitute a different drug and/or composition for the specific composition called for in each of the references.

As noted previously, the Waldrep abstract does nothing to add to the disclosures previously discussed and is highly conjectural in nature. Accordingly, it is respectfully submitted that there is no way that these references can be adequately combined to render Applicants' claims obvious without simply cherry-picking the references for specific bits from each reference by hindsight to reconstruct Applicants' claimed invention. It is too obvious for discussion that this is improper and has been soundly condemned by the courts.

In view of the foregoing amendments and comments, it is respectfully submitted that Applicants' claims as currently pending are now in condition for allowance and have not been shown or suggested under 35 U.S.C. 102 or 35 U.S.C. 103 by any of the references cited taken alone or in combination and such is respectfully solicited.

Respectfully submitted,

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